

# Screening for cervical dysplasia in department of genitourinary medicine

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**SUMMARY** In 632 patients attending a sexually transmitted disease (STD) clinic who were colposcoped because they were in certain high risk groups for cervical neoplasia, and irrespective of cytological findings, 13 out of 51 biopsied had false negative cytology results.

Human papilloma virus (HPV) was the most important sexually transmitted agent associated with cervical intraepithelial neoplasia (CIN), but HPV was also present in most patients with false negative (11/13) and false positive (11/14) cytology results. Screening by colposcopy, as well as cervical cytology, is therefore mandatory and must be available for certain STD clinic patients.

In 1842 Rigoni-Stern noted the protective effect of celibacy against cancer of the uterus (not distinguishing it from the cervix), and subsequent epidemiological studies have stressed the probability of a sexually transmitted factor in cervical carcinogenesis.<sup>1-3</sup> Early age at first intercourse, and multiplicity of partners are important epidemiological features; furthermore, trends in mortality for this cancer closely follow trends in incidence of sexually transmitted disease (STD),<sup>4</sup> so it is logical preventive medicine to screen women attending STD clinics for cervical dysplasia.<sup>5</sup>

Opportunistic screening by cervical cytology started in this department in 1963, to test women at risk who were unlikely to take advantage of other facilities for cervical cytology. Comments on the failure of the community screening programme in England and Wales suggest that the most women who die of carcinoma of the cervix have never had a smear.<sup>6</sup>

In 1983, using the colposcope and taking biopsy specimens where necessary, we started examining women in certain high risk categories. We found, as others had, a number of younger women who, despite having had a recent negative smear result, had developed advanced cervical malignancy.<sup>7</sup>

The principal aim of this study was to assess the incidence and degree of cervical dysplasia in these women, using cytology and colposcopy with biopsy,

and to note discrepancies between these diagnostic methods. The association of cervical dysplasia and the presence of genital warts was studied, and the relevance of age and oral contraceptive usage was considered.

## Patients and methods

Between March 1985 and August 1986, 632 women attending the department of genitourinary medicine in the Royal Liverpool Hospital were colposcoped for the first time. The indications for colposcopy were (a) vulvar, vaginal, or cervical warts found on clinical examination (390); (b) a history of genital warts in the patient's sexual partner (111); (c) previous genital herpes (microbiologically confirmed) in the patient or her partner (38); (d) persistently abnormal findings in cytology smears taken after the treatment of genital infections (48); (e) cervical abnormalities detected on clinical examination (25); (f) a history of promiscuity or postcoital, intermenstrual, or postmenopausal bleeding (20). (Groups a, b, c, e, and f were colposcoped regardless of their cytological status.)

The medical staff had previously obtained the history and carried out the clinical examination. Samples were taken for microbiological screening tests for syphilis and infections with *Nisseria gonorrhoeae*, *Chlamydia trachomatis*, *Candida* spp, *Trichomonas vaginalis*, other vaginal pathogens, and when indicated, herpes simplex virus. Standard laboratory procedures were used to identify the organisms.<sup>8</sup> When necessary, appropriate treatment was given and follow up tests carried out.

Women were asked to advise their sexual partners to

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Table 1 Results of colposcopy screening of 632 women

Indication	No in group	No biopsied (n = 127)	No (% of group) with dysplasia on biopsy (n = 51)	No showing at least CIN III
Genital warts	390	80	28 (7)	12
Sexual contact with genital warts	111	8	1 (1)	1
History of genital herpes	38	4	1 (3)	0
Persistent cervical dyskaryosis on cytology	48	26	20 (42)	8
Clinically abnormal cervix	25	4	1 (4)	1
Other high risk factors*	20	5	0	0

CIN III, cervical intraepithelial neoplasia grade 3.

\*History of promiscuity or postcoital, intermenstrual, or postmenopausal bleeding.

attend STD clinics for investigation and treatment, and the women were given contact cards.

Cervical cytological smears were taken by the medical staff at the first visit unless this was precluded by obvious inflammation of the lower genital tract or heavy menstrual bleeding. Standard techniques were used employing an Ayre's spatula in a single gentle 360° sweep. The material obtained was transferred to a slide, which was flooded with fixative. Cytology reporting was carried out by the university department of obstetrics and gynaecology. Varying degrees of dyskaryosis were reported from mild, through moderate, to severe, which roughly correlated with the grades of cervical intraepithelial neoplasia (CIN) from CIN I to III, as recommended by the recent working party of the British Society for Clinical Cytology.<sup>9</sup> Signs of mild inflammation and wart virus infection were not reported.

All colposcopies were carried out by ABA or IAT using a 120 Zeiss colposcope or OPMI-IFC Zeiss colposcope. Duplication of investigations was avoided by informing the general practitioner briefly (with the patient's permission) of the indication, findings, and further referral, if necessary.

After inspection of the vulva, the cervix was exposed using a bivalve speculum. Any mucus was mopped away, and the cervix, vaginal fornices, and walls were examined both by the naked eye and with the colposcope. When necessary, a repeat smear was taken. Then 5% acetic acid was lavishly applied to the cervix and vaginal walls. Punch biopsy specimens were taken from any suspect (acetowhite) areas of the cervix if the

squamocolumnar junction was visible, using dilating forceps if necessary. Finally, the vaginal fornices and walls were examined, and the speculum was withdrawn. When a biopsy specimen was taken, the woman was asked to return to see the same doctor in three weeks to discuss the results and any further action.

Women were referred to the department of gynaecology for further investigation, and treatment when necessary, if: cervical dysplasia was found in the biopsy specimen; repeat smears showed dyskaryosis despite negative colposcopy or biopsy results (random biopsy specimens were not taken from non-acetowhite areas); in patients with dyskaryosis, colposcopy had been incomplete or unsatisfactory.

## Results

Of 632 women examined by colposcopy in the 16 months from April 1985 to July 1986, 74 had dyskaryotic smears. In 48 of them this dyskaryosis had been the indication for colposcopy, and in the other 26 it was an incidental finding.

Biopsy samples were taken from 127 women because the cervix looked suspect, and 51 (40%) of them showed dysplasia. Table 1 shows the results in the selected groups of patients. (For simplicity, when dyskaryosis or genital warts were present, that indication took precedence over a history of genital herpes or high risk factor in the same woman. No subgroups were employed.) In the 23 women with dysplasia in the absence of genital warts clinically, histological

Table 2 Correlation between results of cytology and histology in 65 women

Dyskaryosis on cytology	Dysplasia on biopsy					Total
	Negative	CIN I	CIN II	CIN III	Cervical cancer	
Negative	0	4	4	4	1	13
Mild (CIN I)	0	0	1	11	0	12
Moderate (CIN II)	13	6	11	7	0	37
Severe (CIN III)	1	0	2	0	0	3
Total	14	10	18	22	1	65

CIN, cervical intraepithelial neoplasia.

evidence of wart virus infection was found in three and of non-specific virus infection in four. Of the 127 women biopsied, 62 with negative smears had negative results. Table 2 shows that, of the remaining 65 women, 38 whose smears had shown dyskaryosis were found to have dysplasia, 13 whose smears had given negative results had dysplasia on biopsy, and 14 with dyskaryotic smears had negative biopsies. (No biopsy specimen had been taken from 22 women with dyskaryotic smears when they were colposcoped). Thus in the 127 women biopsied, the incidence of true positive results on cytology was 75% (38/51), the incidence of true negative results was 82% (62/76), and the incidence of false negative results was 26% (13/51). The overall incidence of false positive results on cytology, including those of women not biopsied, was assumed to be 6% (36/581). Eleven of the 13 women with false negative and 11 of 14 with false positive results had genital warts.

The average age of the 390 women with genital warts was 23; in 31 with cervical dysplasia and cervical condylomata the average age was 26, in 20 with dysplasia but no cervical condylomata it was 28.

When we examined the use of oral contraceptives in women aged under 25 with warts, 85% (11/13) of women with dysplasia and 65% (15/23) of those without dysplasia took the pill, not a significant difference.

## Discussion

Research workers in the past decade have produced evidence to suggest that the human papillomavirus (HPV) is the main sexually transmitted infectious agent associated with cervical dysplasia,<sup>10-12</sup> and up to 30% of women with vulvar condylomata have been reported as having coexistent cervical dysplasia.<sup>13</sup> Table 3 shows that the incidence of women with genital warts increased dramatically in 1971-85 in STD clinics both nationally (4.4-fold) (DHSS, unpublished information) and locally (7.3-fold), increases that were greater than the total increases in new women attenders with STD (2.4-fold nationally, and 2.5-fold in this clinic).

Table 3 *National and local incidences of all sexually transmitted diseases (STDs) and genital warts in women attending STD clinics*

	Year	No of cases of:	
		All STDs	Warts
England and Wales	1971	114 711	4 903
	1985	277 346	21 446
Liverpool	1971	1 436	54
	1985	3 602	395

Although cervical dysplasia was found in at least 16 patients with no clinical, colposcopic, or histological evidence of wart virus infection, our figures confirm the importance of genital warts in association with this condition. There are, however, some difficulties in correlating our cytological and histological results, particularly in patients with genital warts. In fact, in a study of 75 unselected new STD clinic patients, Campion and Oriel found 34 with CIN I-III on biopsy, of whom only 13 had abnormal cytology (Campion MJ, unpublished observation).

Cytological assessment has been described as an inexact and subjective science. Meisels and Fortin commented that, because of the limitations of cytological methods, mild dysplasia could not be distinguished from condylomatous lesions on cytological grounds.<sup>10</sup> Other workers have agreed that assessing wart virus infections may be difficult by cytological, colposcopic, or histological examination alone.<sup>14,15</sup> Similarly, inflammatory cytological changes may be associated with CIN. Toon *et al* found dysplasia in 12.3% of women in whom only non-specific inflammatory changes had been reported.<sup>16</sup>

Mild inflammation was not reported in our patients' cytology results; when inflammation was gross, a repeat smear was requested. Smears had been taken at the first opportunity (with screening tests for genital infection) because compliance of our patients was generally poor. False negative results on cytology may also be due to inadequate cytological sampling.<sup>17</sup> The technique may be improved by using the Aylesbury spatula and cytobrush when indicated. Cytological reporting is now fuller, and includes notification of wart virus infection and inflammatory changes. Although this is contrary to recent recommendations, it alerts the clinicians and enables them to carry out further investigations and, if necessary, treatment.

The effect of penile condylomata in women's sexual partners as a possible explanation of the "male factor" in cervical cancer,<sup>18</sup> because condylomata are sexually transmitted, was not obvious. Many women whose indication for attendance at an STD clinic had been their partner's genital warts, were found on clinical examination to have previously unsuspected warts, and that was their indication for colposcopy. This reduced the "warts contacts" to a group of women without any visible warts on clinical examination.

Herpes simplex virus (HSV) is no longer considered of prime importance in cervical neoplasia,<sup>19</sup> and that was illustrated here. Zur Hausen has suggested that HSV is a mutagen in HPV infected tissue already predisposed to neoplastic change.<sup>20</sup> The prevalence of unrecognised cervical HSV infection without vulvar lesions is not known, and such infection may have accompanied HPV in some patients.

Syrjänen *et al* have said that cervical dysplasia appears in younger women when associated with condylomata.<sup>21</sup> In our STD clinic population, which was much younger on average than the gynaecological patients usually examined, we found this to be so. Women with dysplasia but without warts had a higher mean age than those with dysplasia and warts.

We did not find a significant relation between the use of oral contraception and cervical dysplasia, but in patients aged under 25 who had warts a greater proportion with dysplasia than without dysplasia used the pill. With larger numbers of patients, and by excluding those who used barrier contraception, our findings might have agreed statistically with those of Vessey *et al*, who observed an increased incidence of neoplasia associated with long term use of oral contraception.<sup>22</sup> The hormonal content of the pill has, however, been reduced since the period (1968–74) of that study.

The sexual activity of many women STD clinic patients puts them at risk of cervical neoplasia, and this risk is increased when they have genital warts. It is therefore important to bear in mind that cytology results are unreliable if cervical HPV infection is present, and that cervical inflammation caused by other genital tract infections may also make cytological interpretation difficult.

Thus cytological screening in STD clinics must be backed up by colposcopy of high risk groups. Such facilities should be available in all health regions, at least in the larger STD clinics.<sup>23</sup> The patients and their partners, their varying susceptibility, cofactors, and the progress of dysplasia may be investigated using a combination of cytology, colposcopy, and biopsy, so that treatment may be given when appropriate.

In these investigations, and for the further treatment of many patients, we will continue to co-operate closely with our gynaecological colleagues, from whose expertise many of us have learned. The mutual exchange of junior staff between our two departments would particularly benefit training in both disciplines.

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